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•Case report•

Two cases of neuroleptic malignant syndrome in elderly patients taking atypical antipsychotics

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Summary: Neuroleptic malignant syndrome (NMS) is a rare, life-threatening adverse reaction to antipsychotic medication that typically includes high-fever, extrapyramidal symptoms, autonomic nervous system dysfunction and disturbances in consciousness. Though reported to be more common following use of the older, first generation antipsychotic medications, it can also occur in patients taking the newer, second generation antipsychotic medications. This report discusses the clinical presentation, possible etiology, pathogenesis and treatment of two cases of NMS that occurred in elderly patients after taking atypical antipsychotics. With the increasing use of atypical antipsychotic medication in elderly patients – who may be more susceptible to this adverse reaction – there is a need to increase clinical vigilance about this condition, particularly among internists and gerontologists who may be unfamiliar with this rare complication to antipsychotic medication.

1. Case 1

An 81-year-old male was found unconscious in his home by family members and taken to the emergency department of a general hospital. On admission he was comatose with equal pupils (1mm in diameter), a slow light-reflex, and no reaction to orbital pressure. His temperature was 37 degrees Celsius, pulse was 70 beats per min, respiratory rate was 18 per min, and blood pressure was 140/180 mmHg. The patient's lips were slightly cyanotic and he had sobbing-like breathing, but there were no other abnormalities found on clinical exam of the heart and lungs. His neck was supple and his abdomen was soft. The muscle tension in the limbs was elevated and there was no spontaneous movement of the limbs. There was no response to touch in the limbs though the lower right leg did respond to painful stimuli.

There was no recent history of trauma, allergies, or infections. His previous medical history included: (a) a 30-year history of hypertension that had been controlled at about 140/90 mmHg with amlodipine 5mg/d; (b) a 4-year history of type II diabetes treated with 50 mg acarbose tid (keeping the blood sugar to about 7.8 mmol/L); (c) a 2-year history of Parkinson's disease treated with 125mg benserazide tid; and (d) a 2-month history of visual hallucinations that were being controlled with 1.25 mg olanzapine bid.

Emergency CT head scan on admission showed lacunar lesions in the basal ganglia and brain atrophy. ECG results showed small Q-wave on the third electrode and T-wave changes. Results of the blood-gas analysis was normal, and fasting blood glucose was 6 mmol/L. Laboratory studies identified several abnormalities: troponin T (cTnT) was 0.102 ng/ml (normal: 0.013 to 0.025 ng/ml), myoglobin was >3000 ng/ml (normal for males is 28 to 72 ng/ml), creatine kinase (CPK) was 9986 U/L (normal: 35 to 174 U/L), creatine kinase isoenzyme (CK-MB) was 243 U/L (normal: 0 to 25 U/L); and lactate dehydrogenase (LDH) was 191 U/L (normal: 106 to 211 U/L).

His differential diagnoses on admission to the geriatric medicine ward included coma of unknown origin possible rhabdomyolysis, Parkinson's disease, type-II diabetes and hypertension. After admission, his son returned to the patient's home and discovered that ten 5mg pills of olanzapine were missing, so the possibility of an intentional overdose with olanzapine was also considered and a psychiatric consult was requested. He was given symptomatic treatment to maintain his electrolyte balance and parental nutrition and his condition was monitored. During the second day of admission he developed a painless fever of 39 degrees Celsius without any associated symptoms that

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could explain the fever such as cough, expectoration, abdominal pain, diarrhea, dysuria, swelling of the limbs or joints, or rash. Fecal and urine tests were negative. Blood tests showed a leukocyte level of $9.19x10^9$/L (normal range, 4.5 to $11.0x10^9$/L), with a neutrophil percentage of 73.1% (normal range, 45 to 70%). Physical cooling methods were used to lower his temperature.

When the case was reviewed by a liaison psychiatrist on the second day of admission, the diagnosis was changed to probable NMS. The patient was provided fluids and diuretics and other measures were undertaken to prevent kidney damage (treatment with glutathione and α-keto acid). On the third day of admission, the patient gradually regained consciousness and his body temperature decreased; over the following two weeks his vital signs, temperature and biochemical measures all returned to normal levels. However, soon after he regained consciousness he became emotionally labile with fluctuating depressive and manic symptoms. At one point he experienced hallucinations that were disruptive for other patients so he was given a single intramuscular injection of haloperidol (2.5 mg). After his physical status stabilized (18 days after admission) he made an apparent suicide attempt using scissors so he was transferred to an inpatient psychiatric ward. After one month of treatment on the psychiatric ward he was discharged to his home. The last follow-up of the patient was more than one year after the index discharge; at that time he was being treated with 2.5 mg olanzapine qn and citalopram 20 mg qd (in addition to his hypertensive and diabetes medications). He reported no recurrence of his emotional lability, hallucinations or other symptoms. His medications were being directly managed by his son to decrease the risk of an intentional or unintentional overdose.

2. Case 2

An 85-year-old male came to the emergency department of a general hospital after experiencing tightness in his chest, which his family members had treated with sublingual nitroglycerin. The patient had a history of primary hypertension, severe mitral regurgitation with valve prolapse, and chronic heart failure. In 2002 he had had a dual chamber pacemaker implanted for sick sinus syndrome; this was replaced in January 2010. Immediately before coming to the general hospital, he had been discharged from a psychiatric hospital following 35 days of treatment for Alzheimer's Disease with risperidone (oral solution, 1.4 mg in the morning and 1.2 mg at night). There was no history of trauma, drug allergies, or infectious diseases.

On admission his temperature was 37 degrees Celsius, pulse was 80 beats per min, respiratory was 20 breaths per min, and blood pressure was 105/60 mmHg. The patient was conscious and coherent. His bilateral pupils were of equal size and roundness; he had a reflex to light; he had no cyanosis in his lips and his neck was soft. He had coarse breathing sounds in both lungs without wet or dry rales. Heart rhythm was normal but a holosystolic blowing murmur with grade III intensity and a mid-to-late systole clicking murmur were readily audible in the apical region of the heart. His abdomen was soft. There was no edema in his lower limbs. He had strength in his limbs and his muscle tone was normal. His blood sample showed a leukocyte level of 14.25x109/L, with a neutrophil percentage of 80.6%.

He was admitted to a geriatric ward with admission diagnoses of coronary heart disease, chronic cardiac failure, hypertension, renal insufficiency, and Alzheimer's dementia. He was treated with broad-spectrum antibiotics (meropenem), his regular cardiac medications (digoxin 0.0625 mg/d, spironolactone 25mg/d, perindopril 4mg/d, and metoprolol 12.5mg/d), and risperidone (oral solution, 1.4 mg in the morning and 1.2 mg at night). After four days of hospitalization he experienced a transient loss of consciousness that lasted about 30 seconds. Physical examination at the time revealed a heart rate of 150 beats per min, respiratory rhythm of 24 per min and a blood pressure of 80/50 mmHg. There was no xanthochromia in his skin and sclera. His bilateral pupils were equal in size (3mm in diameter) and roundness; he had a light reflex, a soft neck, and negative cranial nerve reflex; and his upper and lower limbs were symmetrical and had normal muscle tone. Lung CT results showed interstitial post-inflammation changes in both lower lobes, and both sides had a small amount of pleural effusion. ECG results showed depressed ST segments. Echocardiography analysis showed that left ventricle systolic function was normal and left ventricle diastolic function was reduced to a mild extent. Blood biochemical tests showed cTnT=0.165 ng/ml (normal: 0.013 to 0.025 ng/ml), myoglobin=123.6 ng/ml (normal: 28 to 72 ng/ml), CK-MB=4.54 ng/ml (normal: <5 ng/ml), and creatinine=173μmol/L (normal: 50 to 130 μmol/L).

A psychiatric liaison consultant on the fifth day of admission suggested that the low blood pressure was due to the risperidone and recommended stopping the antipsychotic. Two days after his last dose of risperidone the patient's temperature increased to a maximum of 39.1 degrees Celsius. The patient became confused, was uncooperative with a physical examination, had profuse sweating and had twitching of his limbs. His heart rate was 130 beats per min; blood pressure was 98/55 mmHg; coarse sounds without wet or dry rales were heard in the lungs; muscle tension was significantly heightened and the limbs reacted to pain. ECG results showed depressed ST segments similar to the earlier ECG results. Blood tests at that time showed that leukocyte count was $24.42x10^9$/L with a neutrophil percentage of 90%. Blood biochemical tests showed cTnT=0.649 ng/ml, myoglobin=1258 ng/ml (normal <73 ng/ml), CPK=195 U/L, CK-MB=6.42 U/L, LDH=419 U/L, and creatinine=281μmol / L. Three days after his last day of risperidone the patient lapsed into unconsciousness and experienced a rapid drop in blood pressure; despite resuscitative measures his breathing stopped, he went

into cardiac arrest and he died. The diagnosis of 'possible NMS' was considered because, in the absence of X-ray or ECG changes, it was the most probable explanation for the high temperature, profuse sweating, increased muscle tension, and elevated myoglobin.

3. Discussion

3.1 Were these cases of NMS?

The two cases in this report were older men with multiple illnesses taking a variety of medications, who were being treated with atypical antipsychotics prior to the onset of NMS. In both cases, their medical condition and current medications could have slowed the metabolism of antipsychotic medications and, thus, lead to an accumulation of antipsychotics in the body. Case 1 had been taking 1.25 mg of olanzapine twice a day for over two months without apparent problem, but after he took an overdose of 50mg of olanzapine he developed a high fever, loss of consciousness, a drop in blood pressure, a significant elevation in CPK, increased muscle tension, and other symptoms. This patient met all the NMS criteria (see below) and, thus, definitely merited the diagnosis. The patient's sudden increase in dosage with the overdose and the simultaneous interruption in his anti-Parkinson's medication could have precipitated the NMS symptoms.

The diagnosis of NMS in case 2 is somewhat less certain. The patient had been receiving a total daily dose of risperidone of 2.6mg for about a month prior to admission. On admission he had a slightly elevated leukocyte count and a CT scan that showed interstitial post-inflammation changes in his lung. Broad-spectrum antibiotics appeared to resolve the presumed lung infection but the patient subsequently experienced a drop in blood pressure and a brief loss of consciousness so the risperidone was stopped because of the possibility that this was a prelude to a full episode of NMS. However, 24 hours after stopping the risperidone and in the absence of any other changes in the treatment regimen the patient developed a high fever, muscle twitching and fluctuating consciousness. He had a concomitant rise in white blood cell counts and in the blood levels of myoglobin and CPK. The patient's symptoms worsened rapidly over the next day; he subsequently entered a coma and died. This patient had reduced cardiac function, a history of kidney problems (70% of risperidone is metabolized through the kidney), and was regularly taking conventional oral diuretics, so it is certainly possible that his relatively high dose of 2.6mg/d would have accumulated. NMS remains the most likely explanation for his rapid deterioration, despite the termination of risperidone three days before his death.

3.2 Diagnostic criteria of NMS

NMS was first reported in 1960 by the French psychiatrist Delay.[1,2] Almost all of the dopamine antagonists can cause NMS, but the risk of NMS is greater for the typical antipsychotics than for the atypical antipsychotics.[3,4] The reported incidence is less than 0.5% of individuals taking antipsychotic medication.[5] There is a lack of consensus about the diagnostic criteria for NMS but the most commonly used criteria are those provided in DSM-IV:[6]

A) The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication;

B) Two or more of the following: 1) diaphoresis, 2) dysphagia, 3) tremor, 4) incontinence, 5) changes in level of consciousness ranging from confusion to coma, 6) mutism, 7) tachychardia, 8) elevated or labile blood pressure, 9) leukocytosis, 10) laboratory evidence of muscle injury (e.g., elevated CPK);

C) The symptoms in Criteria A and B are not due to another substance (e.g. phencyclidine) or a neurological or other general medical condition (e.g., viral encephalitis);

D) The symptoms in Criteria A and B are not better accounted for by a mental disorder (e.g., mood disorder with catatonic features).

NMS can be divided into three different types depending on the time interval between the initiation of medication and the onset of symptoms: *sudden-onset* (24 to 48 hours after start of medication), *early-onset* (5 to 15 days after start of medication), and *late-onset* (after prolonged usage of medication). NMS can occur at any stage of medication usage, but early-onset NMS is more common with typical antipsychotics and late-onset NMS is more common with atypical antipsychotics; the late-onset type is more difficult to confirm.[7]

3.3 Etiology, risk factors and treatment of NMS

There are two main theories about the pathogenesis of NMS. (a) The *dopamine dysfunction theory* hypothesizes that antipsychotic-induced blockage of dopamine receptors of the hypothalamic pathways, substantia nigra striatal pathways, and midbrain cortical pathways result in altered mental status, high fever, increased muscle tension, sweating, tremors, urinary incontinence, altered consciousness, loss of speech, tachycardia, increased or unstable blood pressure, elevated white blood cell counts and a number of other clinical symptoms.[3] The removal of dopaminergic drugs or lesions to the central dopamine pathway can induce a similar malignant syndrome to NMS. (b) The *skeletal muscle cell metabolism theory*[8] considers the etiology of NMS to be similar to that of malignant hyperthermia; the primary cause is thought to be pathological defects in skeletal muscle such as excessive calcium release by the sarcoplasmic reticulum.

Given the rarity of this condition, it is quite difficult to conduct genetic studies on NMS. There is, however, one study that found an association between NMS and

the cytochrome P450 2D6 enzyme and the D2 receptor gene TaqIA polymorphism.[9]

Many potential risk factors have been considered for NMS. (a) *Demographic Factors*. A high proportion of the patients who develop the late-onset type of NMS are elderly patients, and the male-to-female ratio in these individuals is 2:1.[10] (b) *Physical Factors.* Infection, organic brain disease, dehydration, malnutrition, exhaustion, hyponatremia, thyrotoxicosis, and abuse of alcohol or other psychoactive substances can all increase the risk of NMS.[8,9,11] (c) *Psychological Factors.* Stress, affective disorders, mental retardation, delirium and other types of mental illness are common precursors to the onset of NMS.[12] (d) *Environmental Factors*. High temperatures and high humidity are important factors for the onset of NMS.[12] And (e) *Medications.* A rapid change in antipsychotic dosage or the sudden cessation of antipsychotics can increase the risk of developing NMS for up to 20 days after the change (the peak risk is within 5 days of the change). The concurrent use antipsychotic medications with lithium, anticholinergics, or antidepressants increases the risk of NMS.[8,12] However, the absolute dosage and duration of use of antipsychotics does not have an obvious association with the risk of NMS.

The basic treatment recommendations for confirmed and presumed cases of NMS are to stop antipsychotic medication, closely monitor vital signs, reduce extreme temperatures, infuse fluids, correct electrolyte imbalances, and provide other supportive measures as indicated. NMS is a self-limiting disease, so in most cases the cessation of antipsychotics with symptomatic treatment and supportive care can improve symptoms. Several adjunctive pharmacological and other treatments have been recommended in the treatment of NMS, but there is no general consensus about their effectiveness:[3,13] oral or parental benzodiazepines may promote a more rapid recovery, particularly in patients with mild NMS; dopamine receptor agonists can improve symptoms and shorten recovery time in patients with Parkinson's disease who develop NMS; the muscle relaxant dantrolene can be used to improve fever and muscle rigidity during the acute phase of NMS; and electroconvulsive therapy (ECT) may be effective in patients with NMS who do not respond to medication or supportive treatment.

3.4 Take-home message

The use of atypical antipsychotics is rapidly becoming more widespread, particularly in the elderly population. Many of the elderly patients treated with antipsychotics have multiple illnesses and are taking a variety of medications. Thus their capacity to metabolize antipsychotics may be seriously compromised. All clinicians who treat these patients (geriatricians, internists, neurologists, psychiatrists, and others) need to be vigilant about the possible emergence of the NMS. The neuroleptic malignant syndrome must be considered in the differential diagnosis of all elderly patients who experience episodes of high-fever, extrapyramidal symptoms, autonomic nervous system dysfunction or disturbances in consciousness. Early recognition and rapid treatment of NMS can save lives.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

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